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EFFECT OF AMINO ACID DERIVATIVES OF β-CARBOLINE-3-CARBOXYLATE ON BEHAVIOR IN RATS

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When the possible existence of endogenous anxiogenic compounds is examined, particular attention is drawn to β-carboline derivatives, for in experiments in vivo and in vitro the possibility of their formation in the body has been demonstrated [4, 10, 11], and certain derivatives of β-carboline-3-carboxylate have been shown to possess marked anxiogenic activity [3, 5, 6].

One possible source of β-carbolines in the body may be fragments of peptides with a N-terminal tryptophan residue. Previously the writers synthesized the methyl ester of N-(β-carboline-3-carbonyl) glycine (GA) and the methyl ester of N-(β-carboline-3-carbonyl) leucine (LA) and showed that the action of GA on evoked electrical activity of hippocampal neurons is similar to the action of the known anxiogenic compound β-carboline-3-carboxylate methylamide (FG 7142) [2].

The aim of this investigation was to study the effect of amino-acid derivatives of β-carboline-3-carboxylate on rat behavior.

EXPERIMENTAL METHOD

Experiments were carried out in the fall and winter on male Wistar rats weighing 200-250 g. GA and LA were injected intraperitoneally in the form of a 0.4% solution of a mixture of physiological saline with dimethylformamide (2:1). Control animals received the corresponding volume of a mixture of physiological saline with dimethylformamide (2:1).

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TABLE 1. Effect of GA and LA on Behavior of Rats in Open Field Test

Substance	Dose, mg/kg	Behavioral responses					
		running	visiting center	standing	grooming	defecation	urination
LA	5 (n=9)	21*	1*	1**	0,2*	0,5*	0,2
	10 (n=9)	17*	0,7*	1**	0	0,2*	0
	20 (n=7)	6**	0	0	0	0	0
GA	1 (n=10)	61	1*	4,5*	0,5	2	0,3
	5 (n=10)	23*	1*	0	0	0	0
Control	10 (n=5)	7**	0	0	0	0,2	0
	(n=19)	77	3,1	6,5	0,8	2,1	0,56
	(n=20)	83	2,9	7,3	1,0	1,9	0,7

Legend. *$p < 0.05$, **$p < 0.01$.

The level of locomotor and investigative activity and of emotional reactivity of the rats in a new situation were evaluated by the open field method [7]. Tests began 10 min after injection of the compound. Interspecific aggression was studied on a model of stereotyped behavior of muricidal rats [1]. Muricidal behavior was formed by keeping the rats in social isolation, but with free access to water and food. After 60 days they were tested for muricidal activity. To do this, the rats were kept in a cage containing albino mice. A rat was considered to be muricidal if it killed a mouse within 1 min. When activity of the amino-acid derivatives of β-carboline-3-carboxylate was tested, the number of muricidal rats and the duration of attack on a dead mouse presented to them were recorded.

EXPERIMENTAL RESULTS

GA and LA in doses of 5-20 mg/kg significantly modified the rats' behavior in an open field. In smaller doses, appreciable disturbances of typical forms of behavior were produced only by injection of GA (Table 1). The character of the changes in behavior under the influence of GA and LA was similar. Dose-dependent inhibition of the whole series of orienting and investigative activity and lowering of emotional reactivity took place. The animals examined the arena with the aid of primitive responses, and they remained mainly near to the edge and did not go into the center. Retropulsive responses (backward movements) and various postures of defensive behavior were often exhibited and were easily provoked by the rats. For instance, touching with a stick readily evoked the defensive side position and a vocal response, whereas directing a strong jet of air caused individual animals to adopt a vertical defensive posture. In equal doses, the effects were more easily evoked and were more marked as a result of injection of GA. Thus the effects observed indicate that injection of amino-acid derivatives of β-carboline leads to facilitation of different types of defensive behavior and to inhibition of orienting-investigative activity, evidence of elevation of the "alarm" level.

Since the effects of facilitation of defensive behavior were consistently observed during the action of the substances in a dose of 10 mg/kg, and since no disturbances of locomotion were found under these circumstances, this dose was used to evaluate the effect of GA and LA on the muricidal activity of the rats. GA had a marked inhibitory action on the muricidal activity of the muricidal rats, and was only a little weaker in this respect (Fig. 1) than FG7142, a partial reserve agonist of benzodiazepine receptors [5]. LA had weak activity. Maximal suppression of muricidal behavior was observed 2-3 h after injection. Additionally, after injection of GA in a dose of 10 mg/kg, 3 of the 10 rats adopted a posture of total submission on presentation of a living mouse.

Meanwhile GA and LA equally reduced the duration of attack on a dead mouse presented. Dependence of the duration of attack on the time between injection and the beginning of testing also differed in appearance. When FG 7142 was used, maximal inhibition of aggressiveness was observed 1-3 h after injection. In the case of GA and LA, the duration of attack on a

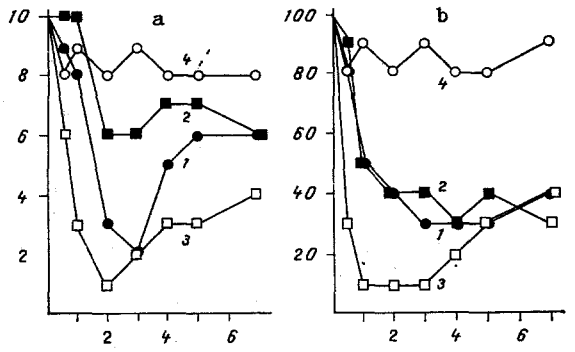

Fig. 1. Dependence of inhibition of muricidal behavior (a) and of duration of attack on a dead mouse presented to the rat (b) on time under the influence of 10 mg/kg of GA (1), LA (2), and FG 7142 (3), and in control (4). For all experiments, n = 10. Abscissa, time of investigation (in h); ordinate, number of muricidal rats (a) and duration of attack (in % of initial value: b).

dead mouse after 2 h was 40% of the control value, at which level it remained throughout the period of observation.

Thus although the general tendency after administration of amino-acid derivatives of β-carboline-3-carboxylate is inhibition of various patterns of interspecific aggressive behavior, there are certain distinguishing features in the activity of GA and LA. This may indicate a similar degree of lowering of the level of the motivational component of muricidal behavior and a different degree of change in the emotional component under the influence of GA and LA. This conclusion is in agreement with our own data showing that GA suppressed orienting and investigative activity by a greater degree than LA, and facilitated provoked defensive behavior.

Considering data obtained previously by the present [1, 2] and other writers [8, 9], to the effect that for anxiogenic compounds of the β-carboline series clear correlation exists between ability to inhibit specific binding of ^{3}H-flunitrazepam, to modify evoked electrical activity of surviving hippocampal slices, and to inhibit orienting and investigative and muricidal activity of rats, it can be concluded that GA is an effective anxiogenic compound. Within the context of the possible role of amino-acid derivatives of β-carboline-3-carboxylate in the formation of anxiety states, the available data, taken as a whole, lead to the conclusion that the most likely candidate in this series for the role of endogenous anxiogenic compound is GA.

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